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UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

THE JOHNS HOPKINS UNIVERSITY, a Maryland corporation, BAXTER HEALTHCARE CORPORATION, a Delaware corporation, and BECTON DICKINSON AND COMPANY, a New Jersey corporation,	:	Case No. 94-105 RRM
Plaintiffs,	:	
v.	:	
CELLPRO, INC., a Delaware corporation,	:	
Defendant.	:	

DECLARATION OF DR. STANLEY CALDERWOOD

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I, STANLEY CALDERWOOD, M.D., do hereby declare:

1. I am the Director of the Autologous Transplant Program, and am also Principal Investigator in the Haploidentical Transplant Program, of the Hospital for Sick Children in Toronto, Ontario, Canada (hereinafter "The Hospital"). The Hospital is dedicated to the treatment of pediatric patients with life-threatening and seriously debilitating illnesses. All of our patients are children.

2. It has now been approximately two years since I and my colleagues at The Hospital began using CellPro's CEPRATE® SC stem cell concentrator for transplant procedures. I would estimate that by now, transplant teams under the supervision of myself or a colleague at The Hospital have performed approximately 65 or 70 transplants, all on pediatric patients, using the CellPro device.

3. CellPro's CEPRATE® SC stem cell concentrator is employed at The Hospital as part of an autologous transplant procedure that entails: (a) concentrating stem and progenitor cells from the patient's peripheral blood or bone marrow; (b) ablating

the patient's marrow with a supra-lethal dose of chemotherapy; and (c) rescuing the patient by reinfusion with the stem and progenitor suspension prepared through use of the CellPro device. This procedure is in regular clinical use at The Hospital for the treatment of childhood malignancies including acute myelogenous leukemia ("AML"), lymphoma, neuroblastoma, soft tissue sarcoma, and brain tumors.

4. Compared to the prior technology for autologous transplantation (by which I mean reinfusion of either the patient's unprocessed bone marrow or the patient's peripheral blood stem cells concentrated by apheresis), use of the CellPro device affords several immediate advantages to both the clinician and the patient, including at least the following:

(A) Lower infusional toxicity. With the prior technology, the volume of suspension needed for reinfusion was relatively large (on the order of 300 ml, in contrast to 5 or 10 ml of a suspension prepared with the CellPro device). In both methods, the suspension needs to be frozen and thawed before use, and in both methods, a reagent known as DMSO must be added to protect the stem cells against damage or death during freezing

and thawing. In both methods, the amount of DMSO added typically amounts to about 10% of the volume of the suspension to be frozen. To a 300 ml volume of transplant suspension, some 30 ml of DMSO would thus be added. When the suspension is eventually infused into the patient, so is the DMSO; and a dose on the order of 30 ml of DMSO is sufficient to cause side effects which may include anaphylactic shock, severe headache, cramps, blood pressure fluctuations and cardiac arrhythmias, among others. When the suspension is prepared using the CellPro device, the amount of DMSO infused into the patient is only on the order of 0.5 to 1 ml (that is, 10% of 5 or 10 ml), and at this very low dosage the side effects are negligible by comparison.

(B) Protection against kidney damage. Marrow and peripheral blood apheresis products contain large populations of red blood cells, which are susceptible to destruction (hemolysis) by DMSO. Hence DMSO-treated marrow and peripheral blood apheresis products typically contain substantial amounts of red-cell debris which can put the patient at risk of renal damage or failure. When

the patient is transplanted with a suspension prepared using the CellPro device, these dangers are avoided.

(C) Lower cost. Because of the infusional toxicity and kidney-damage risks inherent in transplantation therapy with unpurified, DMSO-treated marrow or peripheral blood apheresis product, the process of reinfusing the preparation into the patient was a relatively slow process which consumed time due to the need of staff to attend at the patient's bedside. For example, in the "old days" before we had the CellPro device, a nurse with an anaphylaxis kit was required to be in attendance to monitor and treat DMSO side effects including anaphylactic shock if it occurred. Now, the reinfusion consists simply of the injection of about 20 ml of a stem cell suspension diluted with saline, which is normally uneventful. In addition, costs associated with cryopreservation and storage of the reduced volume product are substantially reduced.

5. In addition there is the theoretical benefit that whereas the prior technology for autologous transplantation risked reinfusing large numbers of tumor cells into the patient, the

CellPro device (because it positively selects cells, including stem and progenitor cells, which are positive to the 12.8 antibody) tends to deplete 12.8-negative tumor cells by leaving them behind in the non-selected population. I call this benefit "theoretical" because it has not yet been determined whether and to what extent the prevention of reinfusion of tumor cells affects long-term survival of the patient. That question will be studied under a recently-submitted grant proposal of mine which would use the CellPro device.

6. In addition to regular clinical use of the CellPro CEPRATE® SC stem cell concentrator in the autologous setting, the device has proved to be of enormous value in the allogeneic setting. By way of historical background, approximately one third of our patients who were otherwise candidates for allogeneic bone marrow transplantation (mostly for acute or chronic leukemias and lymphoma) could not, before the advent of the CellPro device, be transplanted because no suitably matched donor could be found. Although such patients had no other curative therapy available, they were not transplant candidates because if unmatched marrow or apheresed peripheral blood product were infused into such patients, they would invariably die from graft failure or GVHD.

7. With the advent of the CellPro device, however, a means was at hand to purify the transplant suspension by eliminating enough T-lymphocytes (the cells responsible for GVHD) that in many cases a successful allogeneic transplant could be carried out using an imperfectly-matched donor. Thanks to the CellPro device, the percentage of transplant candidates who can feasibly be transplanted has risen from 2/3 to nearly 100%. Under our haploidentical-donor program, pediatric patients who have no other options for curative treatment are now being allogeneically transplanted with suspensions prepared (using the CellPro device) from the marrow or mobilized peripheral blood of haploidentical (half-matched) parents or older siblings. Until the CellPro device made possible these haploidentical transplants, such patients simply had no therapeutic options; they all died.

8. At The Hospital we have recently commenced preclinical trials using CellPro's second-generation product, the CEPRATE® TCD column, a device which carries out a stem- and progenitor-cell enrichment step using the 12.8 antibody, followed by a further T-cell depletion step using a different monoclonal antibody to recognize and select T-lymphocytes. The goal of these new studies is to achieve even further T-cell depletion than the CEPRATE® SC device achieves. The hope is that we can thereby

further reduce GVHD morbidity for allogeneic transplant patients after a haploidentical or other imperfectly matched transplant. There is, in my opinion, no competing T-cell depletion technology that would be a practical replacement of CellPro's TCD column, and we could not feasibly carry out these studies without it.

9. Even for autologous and less critical allogeneic transplant applications, the CellPro devices are, in my estimation, superior to the Baxter Isolex 300 SA device with which The Hospital has had some experience. In our experience, the Baxter device has required an inordinately long time (on the order of 12 hours) to accomplish the processing of suspensions for transplant compared to the CellPro device. Based on our very limited (four patients) experience, yields and purities with the Baxter device were not as good as those achieved with the CEPRATE® SC device.

10. If the CellPro CEPRATE® SC column were for any reason to become unavailable in Canada, clinicians at The Hospital would encounter hardship and patient care would be compromised, at least until a replacement device could be found, procured and put into service. Given the governmental and institutional procedures that would be involved in replacing our CellPro devices, I estimate that the process would take on the order of half a year or more.

Meanwhile, if the CellPro device could not be used, some of our patients, notably those who are candidates for our haploidentical allogeneic transplant program, would be unable to survive the delay in treatment.

11. For the foregoing reasons, I believe that compelling public health interests would be disserved if the CellPro CEPRATE® SC and/or TCD device were to become unavailable in Canada.

I declare upon penalties of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed at Toronto, Ontario, Canada, on this 2d Day of April 1997.

STANLEY CALDERWOOD, M.D.